Attorney Docket No. P63882US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Arne HOLM et al.

Serial No.: 09/408,578 Group Art Unit: 1627

Filed: September 29, 1999 Examiner: T. Wessendorf

For: METHOD FOR PREPARING A LIGAND PRESENTING ASSEMBLY (lpa), AN LPA, AND USES THEREOF

AMENDMENT

Assistant Commissioner of
Patents
Washington, DC 20231

Sir:

Applicants submit the instant Amendment in response to the Office action mailed January 30, 2001.

IN THE CLAIMS

Add the following claims.

--43. The method accroding to claim 1, wherein the LPA obtained is selected from the group consisting of

[LPA-I]: FmocN (CH_2CO-ProValValAlaGluSerProLysLysPro-OH)$_2$,

[LPA-II]: biotin-NH (CH_2) $_5$CON (CH_2CO-ProValValAlaGluSerPro-LysLysPro-OH)$_2$,

[LPA-III]: NH_2CH (Ch_2CO-ProValValAlaGluSerProLysLysPro-OH)$_2$,

[LPA-IV]: H-Lys-NHCH (CH_2CO-ProValValAlaGluSerProLysLysPro-OH)$_2$,

[LPA-VII]: CH_2 (CH_2CO-β-Ala-βAlaLysGluProAsnLysGlyValAsn-ProAspGluValβAla$_2$,

[LPA-VIII]: HC (CH_2CO-LysGluProAsnLysGlyValAsnProAspGlu-ValβAla)$_2$COOH,

[LPA-IX]: Fmoc-NHCH (CH_2CO-AspArgValTyrIleHisProPheHisLeu-NH_2)$_2$,

[LPA-X]: Aloc-NHCH (CH_2CO-AspArgValTyrIleHisProPheHisLeu-NH_2)$_2$, and

[LPA-XI]: Fmoc-AspProThrGlnAsnIleProProGly-NHCH(CH_2CO-AspArgValTyrIleHis-ProPheHisLeu-NH_2)$_2$.

44. The method according to claim 12, wherein the LPA obtained further comprises desired sequence (s) derived from the flagellum of Borrelia burgdorferi or a homologous sequence capable of reacting with antiflagellum antibodies.

45. The method according to claim 16, wherein the LPA obtained is selected from the group consisting of

[LPA-V]: (HO-ProLysLysProSerGluAlaValValPro-$COCH_2$)$_2$CH-NH-Lys(GinLeuAlaAsnAsn-LeuGluThrAlaThrAlaAspTrpLysGlnGlnValGlyGlnTyr-H)$_2$, and

[LPA-VI]: (HO-ProLysLysProSerGluAlaValValPro-$COCH_2$)$_2$N-Lys(AlaSerAlaAlaAlaGlu-IleGlyAlaPheAsnTrpGlnGlnGluThrMet-H)$_2$.

REMARKS

Claims 1-45 are presented for consideration.

Claims 43-45 are added hereby, support for which is found in original claims 28, 30 and 34, as well as examples 7-12 in the specification.

Claims were restricted under 35 U.S.C. §121 to four groupings (i-iiii) of claims. Applicants elect to prosecute Group I, claims 1-18, and new claims 43-45, all drawn to a method of preparing LPA, with traverse.

Pursuant to the requirement for election of species in each of four categories (A-D), Applicants elect as species:

(A)(achiral acid)	iminodiacetic acid (specification page 50).
(B)(sequence)	C-terminal sequence of OspC from *Borrelia burgdorferi*, H-ProValValAla-GluSerProLysLysPro-OH.
(C)(moiety)	biotin-$NH(CH_2)_5CO$.
(D)(LPA)	$FmocN(CH_2CO$-ProValValAlaGluSerProLysLysPro-$OH)_2$, i.e., LPA-I, in new claim 43.

Traversal is maintained with respect to the restriction requirement under §121, between Group I and II. According to the statement of restriction, restriction between Groups I and II is appropriate, allegedly, because "the process as claimed [Group I] can be used to make other and materially different ligands [Group II]." The aforesaid allegation in the statement of restriction is incorrect on its face.

The product (ligand) claims of Group II are defined as "obtainable by the method defined in claim 1" (claim 19, amended). Claim 1 is defined as a method for preparing LPA. Since claim

19 covers any product made by the method of claim 1, the only product that can be made according to method claim 1 (Group I) is the product defined by claim 19 (Group II). Thus, the method claims of Group I cannot be used to make a materially different product than the product defined in Group II.

Since the method claims of Group I cannot be used to make a materially different product than the product defined in Group II, the reason for the restriction between the claims of Group I and Group II is incorrect. Thus, restriction between the two groups is improper and withdrawal of the restriction between the two groups of claims is in order.

Traversal is maintained with respect to the election of species requirement, to the extent that claim 1, identified as generic in the election of species requirement, cannot be sub-divided by restriction. Applicants are entitled to examination of the generic claim; and, if the generic claim is held allowable, Applicants are entitled to dependent claims covering a reasonable number of species covered by the claimed genera.

Favorable action is requested.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:

HOLM et al. Group Art Unit: 1627

Serial No.: 09/408,578 Examiner: T. Wessendoff

Filed: September 29, 1999

For: METHOD FOR PREPARING A LIGAND PRESENTING ASSEMBLY (LPA), AN LPA AND USES THEREOF

AMENDMENT FILED UNDER 37 C.F.R. 1.111

Commissioner of Patents
Washington, D.C. 20231

Sir:

In response to the Office Action mailed July 18, 2001, kindly amend the captioned application as follows:

In the Claims:

Please cancel claims 1-15, 43, and 44 without prejudice or disclaimer.

Please add the following new claims, claims 46-65:

46. (New) A method for preparing a ligand presenting assembly (LPA) for presentation of peptide sequences having free C-terminal groups comprising the steps of

(a) providing by solid phase synthesis or fragment coupling ligands comprising said peptide sequences, the ligands being attached to a solid phase,

(b) deprotecting any protected N-terminal amino groups while the ligands are still attached to the solid phase,

(c) reacting the ligands having unprotected N-terminal amino groups with an achiral di-, tri- or tetracarboxylic acid so as to provide a construct having a ring structure, and

(d) cleaving the construct from the solid phase.

47. (New) A method according to claim 46 further comprising the steps of

(c^1) prior to step (d), deprotecting any N-protected amino groups originating from the carboxylic acid used in step (c),

(c^2) continuing the solid phase synthesis or fragment coupling so as to provide ligands comprising peptide sequences having at least one N-protected N-terminal amino group, and

(c^3) deprotecting any protected N-terminal amino group(s) prior to step (d).

48. (New) The method according to claim 46, wherein the achiral acid used in step (c) is of the general formula

$X[(A)_nCOOH][(B)_mCOOH]$

wherein n and m independently are an integer of from 1 to 20, X is HN, A and B independently are optionally substituted C_{1-10} alkyl, optionally substituted C_{2-10} alkenyl, an optionally substituted cyclic group, an optionally substituted heterocyclic group, or an optionally substituted aromatic group, or A and B together form an optionally substituted cyclic group, an optionally substituted heterocyclic group, or an optionally substituted aromatic group, or

n and m are 0 or an integer of from 1 to 20, X is $H_2N(CR_2)_pCR$, or $RHN(CR_2)_pCR$, wherein p is 0 or an integer of from 1 to 20, wherein each R is H, optionally substituted C_{1-10} alkyl, optionally substituted C_{2-10} alkenyl, an optionally substituted cyclic group, an optionally substituted heterocyclic group, or an optionally substituted aromatic group, and A and B are both optionally substituted C_{1-10} alkyl, optionally substituted C_{2-10}

alkenyl, an optionally substituted cyclic group, an optionally substituted heterocyclic group, or A and B together form an optionally substituted cyclic group, an optionally substituted heterocyclic group, or an optionally substituted aromatic group, or

n and m are 0 or an integer of from 1 to 20, X is $HO(CR_2)_pCR$, $HS(CR_2)_pCR$, halogen-$(CR_2)_pCR$, $HOOC(CR_2)_pCR$, $ROOC(CR_2)_pCR$, $HCO(CR_2)_pCR$, $RCO(CR_2)_pCR$, or $[HOOC(A)_n][HOOC(B)_m]CR(CR_2)_pCR$, wherein p is 0 or an integer of from 1 to 20, each R independently is H, optionally substituted C_{1-10} alkyl, optionally substituted C_{2-10} alkenyl, an optionally substituted cyclic group, an optionally substituted heterocyclic group, or an optionally substituted aromatic group, and A and B are both optionally substituted C_{1-10} alkyl, optionally substituted C_{2-10} alkenyl, an optionally substituted cyclic group, an optionally substituted heterocyclic group, or A and B together form an optionally substituted cyclic group, an optionally substituted heterocyclic group, or an optionally substituted aromatic group, or

n and m are 0 or an integer of from 1 to 20, X is $H_2N(CR_2)_p$, $RHN(CR_2)_p$, $HO(CR_2)_p$, $HS(CR_2)_p$, halogen-$(CR_2)_p$, $HOOC(CR_2)_p$, $ROOC(CR_2)_p$, $HCO(CR_2)_p$, $RCO(CR_2)_p$ or $[HOOC(A)_n][HOOC(B)_m]$, wherein p is 0 or an integer of from 1 to 20, each R independently is H,

optionally substituted C_{1-10} alkyl, optionally substituted C_{2-10} alkenyl, an optionally substituted cyclic group, an optionally substituted heterocyclic group, or an optionally substituted aromatic group, and A and B together form an optionally substituted cyclic group, an optionally substituted heterocyclic group, or an optionally substituted aromatic group.

49. (New) The method according to claim 46, wherein the achiral acid is a di- or tricarboxylic acid.

50. (New) The method according to claim 46, wherein the achiral acid is selected among imino diacetic acid, 2-amino malonic acid, 3-amino glutaric acid, 3-methylamino glutaric acid, 3-chloro glutaric acid, 3-carboxymethyl glutaric acid, 3-methoxy-carbonyl glutaric acid, 3-acetyl glutaric acid, glutaric acid, tricarballylic acid, 3,4-bis-carboxymethyl adipic acid, 4-(2-carboxyethyl)-pimelic acid, (3,5-bis-carboxymethylphenyl)-acetic acid, 3,4-bis-carboxymethyl-adipic acid, benzene-1,2,4,5-tetra carboxylic acid, 4-(3-carboxy-allylamino)-but-2-enoic acid, 4,4'-imino-dibenzoic acid, 1,4-dihydropyridine-3,5-dicarboxylic acid, 5-amino isophthalic acid, 2-chloro malonic acid, 3-hydroxy glutaric acid, and benzene-1,3,5-tricarboxylic acid.

51. (New) The method according to claim 46, wherein the peptide sequences comprise naturally occurring amino acids or non-naturally occurring amino acids or a peptide nucleic acid (PNA) sequence.

52. (New) The method according to claim 47, wherein a chemical entity enhancing the solubility or immunogenicity of the LPA obtained, or being suitable for directing the LPA to its target, or being a marker, is attached to the N-terminal of the achiral carboxylic acid.

53. (New) The method according to claim 52, wherein the chemical entity is selected from fatty acids, antibodies or peptides for directing the LPA to its target, fluorophores, biotin, enzymes such as horse radish peroxidase, alkaline phosphatase and soya bean peroxidase, or nucleic acid sequences.

54. (New) The method according to claim 46, wherein at least one of the peptide sequences comprises all or part of one or more B cell epitopes, all or part of one or more T cell epitopes, or all or part of one or more B and T cell epitopes, or mimics thereof.

55. (New) The method according to claim 54, wherein at least one of the peptide sequences is important for an immune response.

56. (New) The method according to claim 46, wherein at least one of the peptide sequences is derived from OspC protein of *Borrelia burgdorferi*, or is a homologous sequence capable of reacting with anti-OspC antibodies or provoking an immune response.

57. (New) The method according to claim 56, wherein the LPA obtained provide a C-terminal presentation of the C-terminal sequence Pro-Lys-Lys-Pro of OspC.

58. (New) The method according to claim 46, wherein at least one of the peptide sequences is derived from the flagellum of *Borrelia burgdorferi* or is a homologous sequence capable of reacting with anti-flagellum antibodies.

59. (New) The method according to claim 56, wherein the LPA obtained provide C-terminal presentation at least one peptide sequence derived from OspC of *Borrelia burgdorferi* and further comprises at least one peptide sequence derived from the flagellum of *Borrelia burgdorferi*.

60. (New) The method according to claim 46, wherein at least one of the peptide sequences is derived from *Mycobacterium tuberculosis*.

61. (New) The method according to claim 56, wherein the LPA obtained further comprises at least one peptide sequence derived from *Mycobacterium tuberculosis*.

62. (New) The method according to claim 60, wherein at least one of the peptide sequences comprises the ESAT-6, 51-70 sequence protein or the ESAT-6, 1-17 sequence protein of *Mycobacterium tuberculosis*.

63. (New) The method according to claim 46, wherein the LPA obtained is selected from the group consisting of

[LPA-I]: $FmocN(CH_2CO\text{-}ProValValAlaGluSerProLysLysPro\text{-}OH)_2$,

[LPA-II]: $biotin\text{-}NH(CH_2)_5CON(CH_2CO\text{-}ProValValAlaGluSerProLysLysPro\text{-}OH)_2$,

[LPA-III]: $NH_2CH(CH_2CO\text{-}ProValValAlaGluSerProLysLysPro\text{-}OH)_2$,

[LPA-IV]: $H\text{-}Lys\text{-}NHCH(CH_2CO\text{-}ProValValAlaGluSerProLysLysPro\text{-}OH)_2$,

[LPA-VII]: $CH_2(CH_2CO\text{-}\beta\text{-}Ala\text{-}\beta\text{-}AlaLysGluProAsnLysGlyValAsnPro\text{-}AspGluVal\beta Ala)_2$,

[LPA-VIII]: $HC(CH_2CO$-LysGluProAsnLysGlyValAsnProAspGluVal-βAla$)_2COOH$,

[LPA-IX]: Fmoc-$NHCH(CH_2CO$-AspArgValTyrIleHisProPheHisLeu-$NH_2)_2$,

[LPA-X]: Aloc-$NHCH(CH_2CO$-AspArgValTyrIleHisProPheHisLeu-$NH_2)_2$ and

[LPA-XI]: Fmoc-AspProThrGlnAsnIleProProGly-$NHCH(CH_2CO$-AspArg-ValTyrIleHisProPheHisLeu-$NH_2)_2$.

64. (New) The method according to claim 56, wherein the LPA obtained further comprises at least one peptide sequence derived from the flagellum of *Borrelia burgdorferi* or a homologous sequence capable of reacting with anti-flagellum antibodies.

65. (New) The method according to claim 60, wherein the LPA obtained is selected from the group consisting of

[LPA-V]: $(HO$-ProLysLysProSerGluAlaValValPro-$COCH_2)_2CH$-NH-Lys-(GlnLeuAlaAsnAsnLeuGluThrAlaThrAlaAspTrpLysGlnGlnValGlyGlnTyr-$H)_2$, and

[LPA-VI]: $(HO\text{-}ProLysLysProSerGluAlaValValPro\text{-}COCH_2)_2N\text{-}Lys(AlaSer\text{-}AlaAlaAlaGluIleGlyAlaPheAsnTrpGlnGlnGluThrMet\text{-}H)_2$.

REMARKS

The Office Action mailed July 18, 2001, has been received and its contents carefully noted. Claims 1-6, 9-15, 43, and 44 were rejected and claims 16-42, and 45 were withdrawn from consideration. Claims 1-15, 43, and 44 have been canceled and rewritten as new claims 46-65 to more accurately point out what Applicants regard as their invention. Support may be found in the specification generally. No new statutory matter has been added. Reconsideration is respectfully requested.

Objection of Specification

The Examiner objected to the specification because of the recitation of "us of" twice at page 6, line 13.

Applicants have reviewed the specification, in particular, page 6 and can not find the duplicate recitation of "us of". Enclosed herewith is a copy of page 6 of the specification as originally filed. Applicants respectfully request the Examiner's assistance in pointing out the offending phrase.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 1-6 and 9-15 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which Applicant regard as the invention.

Specifically, the Examiner deemed that:

A) the phrases "enabling", "desired sequences", "if necessary, "if present", and "and/or" fail to ascertain the claimed invention with precision;

B) the metes and bounds of "mimics" are indefinite; and

C) claim 10 is indefinite for the recitation of "at least one of the sequences is derived from a sequence …".

Applicants respectfully submit that the claims as amended obviate rejections A and C above. Applicants respectfully submit that the term "mimics" in claim 54 is not indefinite as its scope and meaning is clear to one of skill in the art. Specifically, from the numerous references, patents, and patent applications that disclose peptide mimics and peptide mimetics one of skill in the art would understand that the commonly accepted meaning of a "mimic" or "mimetic" of a peptide refers to a substance that has the essential biological activity of a given peptide. The peptide mimic may be a molecule comprising at least one peptide that mimics elements of the protein secondary structure. A peptide mimic allows the molecular interactions similar to the given peptide. A peptide mimic includes substances that are not peptides but retains the essential biological activity of the given peptide.

As applied in the instant case, the mimics of claim 54, refer to substances that exhibit the biological activity of all or

part of a B cell epitope, all or part of a T cell epitope, or a combination thereof. Therefore, Applicants respectfully submit that the term "mimics" does not render the present claims indefinite and the rejection under 35 U.S.C. 112, second paragraph, should properly be withdrawn.

Claim Objections

The Examiner objected to claims 7-8 (presented herein as new claims 52 and 53) as being improper multiple dependent claims.

Applicants respectfully point out that in the Preliminary Amendment to Lessen Fees filed with the original application on September 29, 1999, claim 7 was amended to be dependent on claim 2 only, as the phrase "according to claims 1-5" in line 3 was deleted. Claim 8 was dependent on claim 7 only. Applicants respectfully submit that claims 7-8 are not improper multiple dependent claims and should have been examined on the merits. Consequently, the claim objections should be withdrawn and claims 52-53 should be examined on the merits.

Election of Species

Applicants respectfully submit that former claims 16-18 and 45, now new claims 60-62 and 65, respectively, are in fact encompassed in Applicants' elected species. Before responding to the specific art rejections, it is important to note that the

present invention relates to ***a method for the preparation*** of an LPA having free C-terminal groups by the use of an ***achiral*** di-, tri-, or tetra-carboxylic acid so as to provide a construct having a ring structure.

The claims clarify that one of the peptide sequences is derived from *Mycobacterium tuberculosis*. Throughout the specification, Applicants disclose and teach that the presented C- and N-terminal sequences may be different. See, for example, the last paragraph of page 31. One of the peptide sequences may be derived from *Mycobacterium tuberculosis* and the other peptide sequence being OpsC derived from *Borrelia burgdorferi*. The C-terminal presented peptide may be OpsC derived from *Borrelia burgdorferi*, and the N-terminal presented peptide may be a sequence derived from *Mycobacterium tuberculosis*. Thus, Applicants respectfully submit that claims 60-62 and 65 are encompassed in the elected species and should be maintained and examined.

Rejection under 35 U.S.C. § 102(a)/102(b)

The Examiner rejected claims 1-6 as being anticipated under 35 U.S.C. 102(a) by Lange et al. or under 102(b) by Gilon et al. or Mihara et al.

Lange et al. relates to the synthesis and activity of dimeric bradykinin antagonists containing diaminodicarboxylic acid bridge residues. Lange et al. teaches the synthesis of short

peptide chains, including up to three amino acids (H-(D-Phe)-Leu-Arg-resin), on a solid support. The free N-terminal amino group (0.2 mmol) was reacted with 0.08 mmol bis(Fmoc)-2,7-diaminosuberic acid (suberic acid = $HOOC(CH_2)_6COOH$) or bis(Fmoc)-2,9-diaminosebacic acid (sebacic acid = $HOOC(CH_2)_8COOH$) using PyBOP and HOBt for 18 hours. Unreacted resin-bound amino groups were then capped with excess acetic anhydride (p. 291, 1st column "Dimeric Petides 4c and 4d").

The method of Lange et al. is decisively different from the method of the present invention. Specifically, the method of Lange et al. requires the use of a coupling dicarboxylic acid comprising two ***chiral*** centers. The claimed methods of the present invention utilize only ***achiral*** dicarboxylic acids to give optically pure products rather than racemic mixtures. Therefore, Lange et al. do not anticipate the present invention as claimed.

Next, Applicants respectfully submit that Gilon et al. deals with ***backbone*** cyclization as a tool for imposing conformational constraint on peptides. The concept and purpose described in Gilon et al. is clearly different from that of the present invention. Gilon et al. provides a process wherein the peptides are synthesized by solid phase peptide synthesis including N-(omega-amino alkylene) Glycine in position 9 and an Arginine in position 6. The cyclic analogs are formed by cyclizing the amino groups of the mentioned amino acids in position 6 and 9 with

dicarboxylic acids, thus forming lactam rings of 17-22 atoms. These lactam rings are completely different from the products of the present invention and the cyclization of Gilon et al. is ***intra***-molecular as compared to ***inter***-molecular cyclization of the present invention. Inter-molecular cyclization avoids the problems of racemisation and further allows the multiple presentation of ligands. The use of achiral acids to provide inter-molecular cyclization reactions and the benefits thereof are not disclosed or taught in Gilon et al. Therefore, Gilon et al. do not anticipate the present invention as claimed.

Mihara et al. concerns peptides with two α-helix segments anchored on 2,2'-bipyridyl-4,4'-dicarboxylic acid. The peptides are synthesized by solid phase synthesis on Kaiser's oxime resin. After completed assembly of the peptide chain on the synthesis resin the peptide is cleaved off the resin and the free peptide reacted with the anchor, Bpy-(beta-Ala)2 or Sub-(beta-Ala)2 with BOP and HOBt ***in DMSO solution*** (Abstract, line 6-7; p. 1134, column 2, line 21 from below) to give peptides with two α-helix segments anchored together.

The anchoring of two peptide chains by ***solution*** synthesis is completely different from the present invention, which is based on ***solid phase cyclization*** of two peptide chains still attached to the synthesis resin. Coupling of two identical residues, such as amines, alcohols, or phenols with a dicarboxylic acid in solution

is a standard operation in a chemical laboratory but the knowledge of such processes can not be used for ***cyclization of two peptide chains with an achiral dicarboxylic acid to give a macrocyclic ring on a solid support*** which is the case in the present invention. Therefore, Mihara et al. does not anticipate the invention as claimed.

As Lange et al., Gilon et al., and Mihara et al, do not anticipate the present invention as claimed, the rejection under 35 U.S.C. 102(a) and (b) should properly be withdrawn.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejected claims 1-6 and 9-15 under 35 U.S.C. 103(a) as being unpatentable over either Mathiesen (WO 97/422210) and Tomalia et al. in view of any one of Lange et al., Gilon et al., or Mihara et al. Specifically, the Examiner deemed that although Mathiesen and Tomalia et al. do not teach cyclization of the linear OspC peptide, one of ordinary skill in the art would be motivated to cyclize the linear peptide using dicarboxylic acid of Lange et al., Gilon et al., or Mihara et al. of cyclization results in a stable peptide. Applicants respectfully submit that the combination of either Mathiesen et al. or Tomalia et al. with or Lange et al., Gilon et al., or Mihara et al., fail to alleviate the deficiencies in the disclosures of Lange et al., Gilon et al., or Mihara et al. Hence, the combinations cannot render the present

invention as claimed obvious.

The disclosures of the prior art, alone or in combination, do not disclose, teach, or suggest forming a macrocyclic ring system by reacting the N-terminal amino group of two identical peptide chains comprising at least 15 amino acids each and still attached to the synthesis resin with an achiral dicarboxylic acid.

The state of the art of amino acid bridging techniques can be learned from the 1993 report by Alberts et al. (Ref. 17 cited in the present specification) which teaches that bridging with a half equivalent 2,7-bis(Boc-amino) suberic acid coupled to one equivalent of lysine (2Cl-Z-protected) attached to the synthesis resin is slow and takes place over up to 4 days (p. 358, line 14). Thus, ring formation of longer amino acid sequences may be similar or more difficult requiring activation conditions, which could prevent formation of well-defined products with optically active bridging compounds.

Therefore, at the time of the priority of the present invention it would not have been obvious to one of ordinary skill in the art that a macrocyclic ring system could be formed with a reasonable expectation of success by reacting the N-terminal amino group of two identical peptide chains still attached to the synthesis resin and with at least up to 15 amino acids in each chain (LPA-VII), with an achiral dicarboxylic acid. On the

contrary, the slow reactions described with very short chains (1 to 3 amino acids), as cited above, pointed to the opposite. The reasons for this difference is not known but it may be due to the particular amino acids used in the above cited works. In the present invention, achiral dicarboxylic or tricarboxylic acids are used in order to avoid racemization problems which arise where longer or higher coupling activation with the dicarboxyl acid is necessary.

Nowhere in the cited prior art is the use of achiral carboxylic acids taught or suggested in a process for solid phase cyclization. As the cited prior art, alone or in combination, do not result in the present invention as claimed, a *prima facie* case has not been established. As the Examiner has not established a *prima facie* case of obviousness, the rejection under 35 U.S.C. §103(a) should properly be removed.

CONCLUSION

Accordingly, in view of the foregoing amendments and remarks, the Examiner is respectfully requested to reconsider and withdraw the rejection of the claims and to find this application to be in allowable condition.

If the Examiner believes that a conference would be of value in expediting the prosecution of this application, the Examiner is invited to telephone the undersigned to arrange for such a conference.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:

HOLM et al. Group Art Unit: 1627

Serial No.: 09/408,578 Examiner: T. Wessendoff

Filed: September 29, 1999

For: METHOD FOR PREPARING A LIGAND PRESENTING ASSEMBLY (LPA), AN LPA AND USES THEREOF

RESPONSE TO NOTICE TO COMPLY WITH SEQUENCE LISTING REQUIREMENTS

Commissioner of Patents
Washington, D.C. 20231

Sir:

In response to the Office Action mailed April 5, 2002, kindly amend the captioned application as follows:

In the Specification:

Please replace pages 6, 7, 30, 31, 33, 35, 36, 39 and 50-59 of the specification with the same numbered substitute specification pages appended hereto.

In the Sequence Listing:

Please replace the Sequence Listing filed October 2, 2000, for the above-identified application with the Substitute Sequence Listing appended hereto.

In the Claims:

Please amend claims 57, 62, 63, and 65 as follows:

57. (Amended) The method according to claim 56, wherein the LPA obtained provides a C-terminal presentation of the C-terminal sequence Pro-Lys-Lys-Pro (Seq. ID 7) of OspC.

62. (Amended) The method according to claim 60, wherein at least one of the peptide sequences comprises the ESAT-6, 51-70 sequence or the ESAT-6, 1-17 sequence protein HO-GlnLeuAlaAsnAsnLeu-GluThrAlaThrAlaAspTrpLysGlnGlnValGlyGlnTyr-H (HO-Seq. ID 2-H) of *Mycobacterium tuberculosis* HO-AlaSerAlaAlaAlaGluIleGlyAlaPheAsn-TrpGlnGlnGluThrMet-H (HO-Seq. ID 3-H).

for preparing an

63. (Amended) The method according to claim 46[, wherein the] LPA [obtained is] selected from the group consisting of

[LPA-I]: FmocN(CH_2CO-ProValValAlaGluSerProLysLysPro-OH)$_2$ (FmocN(CH_2CO-Seq. ID 1-OH)$_2$),

[LPA-II]: biotin-NH$(CH_2)_5$CON(CH_2CO-ProValValAlaGluSerProLysLysPro-OH)$_2$ (biotin-NH$(CH_2)_5$CON(CH_2CO-Seq. ID 1-OH)$_2$),

[LPA-III]: $NH_2CH(CH_2CO$-ProValValAlaGluSerProLysLysPro-$OH)_2$ ($NH_2CH(CH_2CO$-Seq. ID 1-$OH)_2$),

[LPA-IV]: H-Lys-$NHCH(CH_2CO$-ProValValAlaGluSerProLysLysPro-$OH)_2$ (H-Lys-$NHCH(CH_2CO$-Seq. ID 1-$OH)_2$),

[LPA-VII]: $CH_2(CH_2CO$-β-Ala-β-AlaLysGluProAsnLysGlyValAsnPro-AspGluValβAla-$OH)_2$ ($CH_2(CH_2CO$-β-Ala-β-Ala-Seq. ID 4-βAla-$OH)_2$),

[LPA-VIII]: $HC(CH_2CO$-LysGluProAsnLysGlyValAsnProAspGluVal-βAla$)_2COOH$ ($HC(CH_2CO$-Seq. ID 4-βAla$)_2COOH$),

[LPA-IX]: Fmoc-$NHCH(CH_2CO$-AspArgValTyrIleHisProPheHisLeu-$NH_2)_2$ (Fmoc-$NHCH(CH_2CO$-Seq. ID 5-$NH_2)_2$),

[LPA-X]: Aloc-$NHCH(CH_2CO$-AspArgValTyrIleHisProPheHisLeu-$NH_2)_2$ (Aloc-$NHCH(CH_2CO$-Seq. ID 5-$NH_2)_2$) and

[LPA-XI]: Fmoc-AspProThrGlnAsnIleProProGly-$NHCH(CH_2CO$-AspArg-ValTyrIleHisProPheHisLeu-$NH_2)_2$ (Fmoc-Seq. ID 6-$NHCH(CH_2CO$-Seq. ID 5-$NH_2)_2$).

65. (Amended) The method according to claim 60, wherein the LPA obtained is selected from the group consisting of

[LPA-V]: $(HO\text{-}ProLysLysProSerGluAlaValValPro\text{-}COCH_2)_2CH\text{-}NH\text{-}Lys\text{-}(GlnLeuAlaAsnAsnLeuGluThrAlaThrAlaAspTrpLysGlnGlnValGlyGlnTyr\text{-}H)_2$ $((HO\text{-}Seq.\ ID\ 12\text{-}COCH_2)_2CH\text{-}NH\text{-}Lys\text{-}(Seq.\ ID\ 2\text{-}H)_2)$, and

[LPA-VI]: $(HO\text{-}ProLysLysProSerGluAlaValValPro\text{-}COCH_2)_2N\text{-}Lys(AlaSer\text{-}AlaAlaAlaGluIleGlyAlaPheAsnTrpGlnGlnGluThrMet\text{-}H)_2$ $((HO\text{-}Seq.\ ID\ 12\text{-}COCH_2)_2N\text{-}Lys(Seq.\ ID\ 3\text{-}H)_2)$.

REMARKS

The Office Action mailed April 5, 2002, has been received and its contents carefully noted. The application was deemed to have failed to comply with the Sequence Listing Requirements.

Applicants respectfully submit that the specification and claims as amended herein conform to the Sequence Listing Requirements. Support may be found in the specification generally. No statutory new matter has been added. Reconsideration is respectfully requested.

Applicants note that some sequences are sometimes listed in an unconventional order, C-terminal to N-terminal order.

Submission of Substitute Sequence Listing

In connection with the Substitute Sequence Listing submitted herewith, the undersigned hereby states that:

1. In accordance with 37 C.F.R. 1.825(a), the Substitute Sequence Listing does not contain new matter.
2. In accordance with 37 C.F.R. 1.825(b), the content on the attached paper copy and the attached computer readable copy of the Substitute Sequence Listing are the same.
3. All the statements made herein are true and that

all statements made on information and belief are believed to be true, and that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

Applicants also enclose herewith two floppy disks containing the computer readable form of the Substitute Sequence Listing and a copy of the Notice to File Corrected Application Papers.

Petition for Extension of Time

A Petition for an Extension of Time for Two (2) months under 37 CFR §1.136 and the appropriate fee under 37 CFR § 1.17 are filed herewith to extend the due date for responding to the Official action to July 5, 2002.

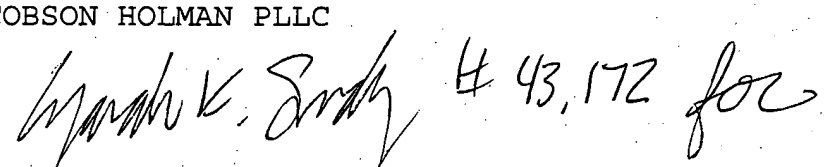
CONCLUSION

Accordingly, in view of the foregoing amendments, the Examiner is respectfully requested to reconsider and withdraw the rejection of the claims and to find this application to be in allowable condition.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached pages are captioned **"Version With Markings To Show Changes Made To Claims"**, **"Substitute Pages Of The Specification"** and **"Version With Markings To Show Changes Made To Specification"**.

If the Examiner believes that a conference would be of value in expediting the prosecution of this application, the Examiner is invited to telephone the undersigned to arrange for such a conference.

Respectfully submitted,
JACOBSON HOLMAN PLLC

By 

Harvey B. Jacobson, Jr.
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Date: July 5, 2002
Atty. Docket: 162/P63882US0

Version With Markings To Show Changes Made To Claims

57. (Amended) The method according to claim 56, wherein the LPA obtained [provide] provides a C-terminal presentation of the C-terminal sequence Pro-Lys-Lys-Pro (Seq. ID 7) of OspC.

62. (Amended) The method according to claim 60, wherein at least one of the peptide sequences comprises the ESAT-6, 51-70 sequence or the ESAT-6, 1-17 sequence protein HO-GlnLeuAlaAsnAsnLeu-GluThrAlaThrAlaAspTrpLysGlnGlnValGlyGlnTyr-H (HO-Seq. ID 2-H) of *Mycobacterium tuberculosis* HO-AlaSerAlaAlaAlaGluIleGlyAlaPheAsn-TrpGlnGlnGluThrMet-H (HO-Seq. ID 3-H).

63. (Amended) The method according to claim 46, wherein the LPA obtained is selected from the group consisting of

[LPA-I]: $FmocN(CH_2CO\text{-}ProValValAlaGluSerProLysLysPro\text{-}OH)_2$ ($FmocN(CH_2CO\text{-}$Seq. ID 1-$OH)_2$),

[LPA-II]: $biotin\text{-}NH(CH_2)_5CON(CH_2CO\text{-}ProValValAlaGluSerProLysLysPro\text{-}OH)_2$ ($biotin\text{-}NH(CH_2)_5CON(CH_2CO\text{-}$Seq. ID 1-$OH)_2$),

[LPA-III]: $NH_2CH(CH_2CO\text{-}ProValValAlaGluSerProLysLysPro\text{-}OH)_2$ ($NH_2CH(CH_2CO\text{-}$Seq. ID 1-$OH)_2$),

[LPA-IV]: H-Lys-NHCH(CH_2CO-ProValValAlaGluSerProLysLysPro-OH)$_2$ (H-Lys-NHCH(CH_2CO-Seq. ID 1-OH)$_2$),

[LPA-VII]: CH_2(CH_2CO-β-Ala-β-AlaLysGluProAsnLysGlyValAsnPro-AspGluValβAla-OH)$_2$ (CH_2(CH_2CO-β-Ala-β-Ala-Seq. ID 4-βAla-OH)$_2$),

[LPA-VIII]: HC(CH_2CO-LysGluProAsnLysGlyValAsnProAspGluVal-βAla)$_2$COOH (HC(CH_2CO-Seq. ID 4-βAla)$_2$COOH),

[LPA-IX]: Fmoc-NHCH(CH_2CO-AspArgValTyrIleHisProPheHisLeu-NH_2)$_2$ (Fmoc-NHCH(CH_2CO-Seq. ID 5-NH_2)$_2$),

[LPA-X]: Aloc-NHCH(CH_2CO-AspArgValTyrIleHisProPheHisLeu-NH_2)$_2$ (Aloc-NHCH(CH_2CO-Seq. ID 5-NH_2)$_2$) and

[LPA-XI]: Fmoc-AspProThrGlnAsnIleProProGly-NHCH(CH_2CO-AspArg-ValTyrIleHisProPheHisLeu-NH_2)$_2$ (Fmoc-Seq. ID 6-NHCH(CH_2CO-Seq. ID 5-NH_2)$_2$).

65. (Amended) The method according to claim 60, wherein the LPA obtained is selected from the group consisting of

[LPA-V]: (HO-ProLysLysProSerGluAlaValValPro-$COCH_2$)$_2$CH-NH-Lys-(GlnLeuAlaAsnAsnLeuGluThrAlaThrAlaAspTrpLysGlnGlnValGlyGlnTyr-H)$_2$ ((HO-Seq. ID 12-$COCH_2$)$_2$CH-NH-Lys-(Seq. ID 2-H)$_2$), and

[LPA-VI]: (HO-ProLysLysProSerGluAlaValValPro-$COCH_2$)$_2$N-Lys(AlaSer-AlaAlaAlaGluIleGlyAlaPheAsnTrpGlnGlnGluThrMet-H)$_2$ ((HO-Seq. ID 12-$COCH_2$)$_2$N-Lys(Seq. ID 3-H)$_2$).

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
Arne HOLM et al.	Art Unit: 1639
Serial No.: 09/408,578	Examiner: T.D. Wessendorf
Filed: September 29, 1999	Atty. Docket: P63882US0
For: METHOD FOR PREPARING A LIGAND PRESENTING ASSEMBLY (LPA), AN LPA AND USES THEREOF	

RESPONSE UNDER 37 C.F.R. 1.111

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

This is in response to the Office Action mailed October 21, 2002.

AMENDMENT

In the claims:

Please cancel claims 16-42 and 46-65.

Please add new claims 66-83 as follows:

66. (New) A method for preparing a ligand presenting assembly (LPA) for presentation of peptide sequences having free C-terminal groups comprising the steps of

(a) providing by solid phase synthesis or fragment coupling ligands comprising said peptide sequences, the ligands being attached during the synthesis to a solid phase,

(b) deprotecting any protected N-terminal amino groups while the ligands are still attached to the solid phase,

(c) reacting the ligands having unprotected N-terminal amino groups with an achiral dicarboxylic acid being N-protected on any amino or imino groups so as to provide a construct having a ring structure comprising said carboxylic acid and two ligands comprising said peptide sequences, and

(d) cleaving the construct from the solid phase.

67. (New) A method according to claim 66 further comprising the steps of

(c^1) prior to step (d), deprotecting any N-protected amino or imino groups originating from the carboxylic acid used in step (c),

(c^2) continuing the solid phase synthesis or fragment coupling so as to provide ligands comprising peptide sequences having at least one N-protected N-terminal amino group, and

(c^3) deprotecting any protected N-terminal amino group(s) prior to step (d).

68. (New) The method according to claim 66, wherein the achiral acid used in step (c) is of the general formula

$X[(A)_nCOOH][(B)_mCOOH]$

wherein n and m independently are an integer of from 1 to 5, X is HN, A and B independently are C_{1-10} alkyl, C_{2-10} alkenyl, or a cyclic group.

69. (New) The method according to claim 66, wherein the achiral acid is imino acetic acid.

70. (New) The method according to claim 66, wherein the achiral acid is selected among imino diacetic acid, 2-amino malonic acid, 3-amino glutaric acid, glutaric acid, and tricarballylic acid.

71. (New) The method according to claim 66, wherein the peptide sequences comprise naturally occurring amino acids or non-naturally occurring amino acids or a peptide nucleic acid (PNA) sequence.

72. (52) The method according to claim 66, further comprising the step of

(b^1) prior to step (c), attaching a chemical entity selected from fatty acids, antibodies or peptides for directing the LPA to its target, fluorophores, biotin, enzymes, or nucleic acid sequences, to the N-terminal of the achiral dicarboxcylic acid.

73. (New) The method according to claim 72, wherein the chemical entity is biotin-$NH(CH_2)_5CO$.

74. (New) The method according to claim 66, wherein at least one of the peptide sequences comprises all or part of one or more B cell epitopes, all or part of one or more T cell epitopes, or

all or part of one or more B and T cell epitopes, or mimics thereof.

75. (New) The method according to claim 74, wherein at least one of the peptide sequences is important for an immune response.

76. (New) The method according to claim 66, wherein at least one of the peptide sequences is derived from OspC protein of *Borrelia burgdorferi*.

77. (New) The method according to claim 66, for preparing an LPA for presentation of the C-terminal sequence Pro-Lys-Lys-Pro (Seq. ID 7) of OspC.

78. (New) The method according to claim 66, wherein at least one of the peptide sequences is derived from the flagellum of *Borrelia burgdorferi*.

79. (New) The method according to claim 66, for preparing an LPA for presentation at least one peptide sequence derived from OspC of *Borrelia burgdorferi* which further comprises at least one peptide sequence derived from the flagellum of *Borrelia burgdorferi*.

80. (New) The method according to claim 66, for preparing an LPA selected from the group consisting of

[LPA-I]: $FmocN(CH_2CO\text{-}ProValValAlaGluSerProLysLysPro\text{-}OH)_2$,

[LPA-II]: $biotin\text{-}NH(CH_2)_5CON(CH_2CO\text{-}ProValValAlaGluSerProLysLysPro\text{-}OH)_2$,

[LPA-III]: $NH_2CH(CH_2CO$-ProValValAlaGluSerProLysLysPro-$OH)_2$,

[LPA-IV]: H-Lys-$NHCH(CH_2CO$-ProValValAlaGluSerProLysLysPro-$OH)_2$,

[LPA-VII]: $CH_2(CH_2CO$-β-Ala-β-AlaLysGluProAsnLysGlyValAsnPro-AspGluValβAla$)_2$,

[LPA-VIII]: $HC(CH_2CO$-LysGluProAsnLysGlyValAsnProAspGluVal-β$Ala)_2COOH$,

[LPA-IX]: Fmoc-$NHCH(CH_2CO$-AspArgValTyrIleHisProPheHisLeu-$NH_2)_2$,

[LPA-X]: Aloc-$NHCH(CH_2CO$-AspArgValTyrIleHisProPheHisLeu-$NH_2)_2$ and

[LPA-XI]: Fmoc-AspProThrGlnAsnIleProProGly-$NHCH(CH_2CO$-AspArg-ValTyrIleHisProPheHisLeu-$NH_2)_2$.

81. (New) A method for preparing a ligand presenting assembly (LPA) for presentation of peptide sequences from Borrelia burgdorferi having free C-terminal groups comprising the steps of

(a) providing by solid phase synthesis or fragment coupling ligands comprising said peptide sequences, the ligands being attached during the synthesis to a solid phase,

(b) deprotecting any protected N-terminal amino groups while the ligands are still attached to the solid phase,

(c) reacting the ligands having unprotected N-terminal amino groups with an achiral dicarboxylic acid so as to provide a

construct having a ring structure comprising said carboxylic acid and two ligands comprising said peptide sequences, and

(d) cleaving the construct from the solid phase.

82. (New) A method for preparing a ligand presenting assembly (LPA) for presentation of peptide sequences derived from OcpC protein of Borrelia burgdorferi having free C-terminal groups comprising the steps of

(a) providing by solid phase synthesis or fragment coupling ligands comprising said peptide sequences, the ligands being attached during the synthesis to a solid phase,

(b) deprotecting any protected N-terminal amino groups while the ligands are still attached to the solid phase,

(c) reacting the ligands having unprotected N-terminal amino groups with an achiral dicarboxylic acid so as to provide a construct having a ring structure comprising said carboxylic acid and two ligands comprising said peptide sequences, and

(d) cleaving the construction from the solid phase.

83. (New) A method for preparing a ligand presenting assembly (LPA) for presentation of peptide sequences derived from the flagellum of Borrelia burgdorferi having free C-terminal groups comprising the steps of

(a) providing by solid phase synthesis or fragment coupling ligands comprising said peptide sequences, the ligands being attached during the synthesis to a solid phase,

(b) deprotecting any protected N-terminal amino groups while the ligands are still attached to the solid phase,

(c) reacting the ligands having unprotected N-terminal amino groups with an achiral dicarboxylic acid so as to provide a construct having a ring structure comprising said carboxylic acid and two ligands comprising said peptide sequences, and

(d) cleaving the construct form the solid phase.

REMARKS

The Office Action mailed October 21, 2002, has been received and its contents carefully noted. The pending claims were claims 16-42 and 45-65. Claims 46-59 and 63-64 were rejected. Claims 16-42, 45, 60-62, and 65 were withdrawn from consideration. By this amendment, claims 16-42 and 45-65 have been cancelled, and claims 66-83 have been added. Support may be found in the specification and claims as originally filed. No statutory new matter has been added. Reconsideration is respectfully requested.

Claim Amendments

Applicants note that the new claims correspond to the former claims as follows:

1. New claims 66-79 correspond to former claims 46-59, respectively.
2. New claim 80 corresponds to former claim 63.
3. New claims 81-83 are newly proposed. Applicants submit new claims 66-68 on specific embodiments for representation of peptide sequences from Borrelia burgdorferi.

Rejection under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 46-59 and 63-64 under 35 U.S.C. 112, first paragraph because the Examiner deemed that the specification, while being enabling for the antigenic peptide sequence of Borrelia burgdorferi and iminodiacetic acid as the bridging group, the specification does not reasonably provide enablement for any type of ligand presenting assembly containing any peptide chain or its homologs or mimics, with any achiral di or tri or tetra carboxylic acid as a bridging group and any type of chemical moiety, target or marker group that elicits an

immune response under any given conditions of synthesis. The Examiner deemed that Applicants' broad steps of synthesis using any achiral dicarboxylic acid is nothing more than an invitation to experiment in the hope that a discovery can be made. The Examiner further stated that the specification does not teach any tri or tetracarboxylic acid as employed in the instant method.

Applicants submit that claims 46-50 have further been restricted to involve achiral dicarboxylic acids only. This means also that claim 49 has been restricted to the elected species imino acetic acid, and that claim 50 has been restricted to the dicarboxylic acids, the use of most of them being illustrated in the examples.

Applicants respectfully submit that the claims as presented are substantially limited to the use of simple achiral dicarboxylic acids as the bridging group (claims 66 and 68-70). The general applicability of these acids is illustrated with imino diacetic acid (Examples 1, 2 and 6), 3-amino glutaric acid (Examples 3, 4 and 5), glutaric acid (Examples 7, 9. 10 and 11) and tricarballylic acid (Example 8). Please note that although tricarballylic acid is in fact a tricarboxylic acid, it is used as a dicarboxylic acid, see e.g. Example 8, wherein the surplus carboxy group is available for subsequent coupling.

Furthermore, Applicants submit that the general applicability of the method of the invention for preparing LPA for presentation of peptide sequences has been illustrated for a wide number of sequences from different sources, for example, Borrelia burgdorferi (Examples 1-5), Mycobacterium tuberculosis (Examples 5-6), Chlamydia trachomatis (Examples 7-8 and Chlostridium thermosacchrolyticum (Example 12), as well as sequences derived from angiotensin-I (Examples 9-12).

Applicants also submit herewith a journal article, Roberts, D.M., *et al.* (2002) "Environmental regulation and differential production of members of the Bdr protein family of Borrelia burgdorferi" Infect. Immun. 70:7033-7041, which provides that experiments that allow the synthesis of five further peptide sequences from Borrelia burgdorferi. See p. 7034, right column, beginning at line 6, and Table 2.

Accordingly, no undue experimentation is necessary and only routine synthetic methods known in the art are necessary. Therefore, Applicants respectfully submit that the claims as pending are enabled and the rejection under 35 U.S.C. 112, first paragraph, should properly be withdrawn.

Rejection under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 46-65 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner deemed that:

1. Claim 46 is incomplete for omitting essential steps, such omission amounting to a gap between the steps and that claim 47 step (c') is unclear since claim 6 step c does not recite that the dicarboxylic acid is protected at its N-terminus.

2. Claim 52 is inconsistent and broadens the base claim 46. The base claim does not recite for an additional chemical entity at the N-terminus of the achiral carboxylic acid and recites an N-protected group. The metes and bounds of the chemical entity, target and market, within the claimed context, are indefinite.

3. Claim 53 is indefinite for reciting the phrase "such as" because it is unclear whether the limitations following the phrase are part of the claimed invention.

4. Claim 54 is unclear as to the metes and bounds of the B or C epitopes of the peptide sequences, the combination of these epitopes or mimics thereof and furthermore it is not clear within the claimed context, "mimics" thereof i.e., in what context the peptide sequences is considered a mimic.

5. Claim 55 is unclear as to the basis by which a peptide sequence is considered to be "important" for an immune response.

6. Claims 56 and 57 are indefinite as the metes and bound of the homologous sequence are unclear especially since it is uncertain whether, in fact said sequence is "capable of reacting with the antibodies or provoking an immune response". Furthermore, it is not clear how a peptide sequence is derived from the OspC protein.

7. Claim 57 is indefinite in the recitation of LPA since claim 56 recites peptide sequences. Furthermore the language "C-terminal presentation of the C-terminal sequence" is confusing.

8. Claim 59 is confusing in its language especially since claim 56 does not recite LPA but peptide sequence.

9. Claim 64 is a duplicate of claim 58.

Applicants respectfully submit that the phrase "being attached" in claim 66, step (a), is not unclear, since it is commonly known in the art that during a solid phase synthesis the construct is temporarily attached to the solid phase, and, in the present claim it is stated that the construct is cleaved from the solid phase in step (d). The description also provides sufficient information for a person skilled in the art to

understand the scope and meaning of the claim. Accordingly, the phrase "during the synthesis" is in fact superfluous.

Applicants respectfully submit that the claims as amended obviate the remaining rejections under 35 U.S.C. 112, second paragraph. Therefore, the rejection under 35 U.S.C. 112, second paragraph, should properly be withdrawn.

Rejection under 35 U.S.C. § 102(a)

The Examiner rejected claims 46-51 under 35 U.S.C. 102(a) as being anticipated by Lange et al. (J Pept. Sci.) or 35 U.S.C. 102(b) by Gilon et al. (Pept. Chem., Proc. Jpn. Symp.) for reasons advanced in the last Office Action. Specifically, the Examiner deemed the claims did not differentiate an intra from intermolecular cyclization and that there is nothing in the broad claimed method steps that lead to an intermolecular cyclization of the product.

Applicants respectfully submit that the present claims have been limited to a construct having a ring structure comprising the carboxylic acid and two ligands comprising the peptide sequences, viz. and intermolecular cyclization. Furthermore, the scope of the claimed dicarboxylic acids has been restricted to simple acids.

As neither Lange et al. nor Gilon et al. teach or suggest a construct having a ring structure comprising the carboxylic acid and two ligands comprising the peptide sequences, the present invention as claimed is novel and the rejection under 35 U.S.C. 102(a) should properly be withdrawn.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejected claims 56-59 and 63-64 under 35 U.S.C. 103(a) as being unpatentable over Mathiesen and Tomalia et al. in view of Gilon et al. or Lange et al. Specifically, the

Examiner deemed that the Applicants' arguments were not commensurate in scope with at least the broad claim 46.

Applicants respectfully submit that Mathiesen discloses a method of making a peptide from a sequence of OspC of Borrelia burgdorferi. Tomalia also discloses a method of making a peptide. However, as the Examiner admits in the Office Action dated 18 July 2001, none of these references teach the cyclization of the peptide.

Applicants submit that Gilon et al. discloses backbone cyclization involving the formation of lactam rings, viz. a totally different ring structure than the one used in the present application as claimed. This substantial difference between the present invention and the prior art is clearly expressed in the present claims. Nowhere does Gilon et al. teach or suggest making or using the ring structure of the presently claimed invention, a ring structure comprising carboxylic acid and two ligands comprising the peptide sequences. As lactam rings are different from the ring structures of the present invention, one of ordinary skill in the art would not be motivated to make the peptides of Mathiesen and Tomalia et al. into ring structures using the cyclization method of Gilon et al. with a reasonable likelihood of success in obtaining the ring structure of the present invention, comprising carboxylic acid and two ligands comprising the peptide sequences. Therefore, the combination of Mathiesen and Tomalia et al. and Gilon et al. do not render obvious the present invention as claimed and the rejection under 35 U.S.C. 103(a) should properly be withdrawn.

Applicants further submit that the scope of the work disclosed by Lange et al. is synthesis and activity of dimeric bradykinin antagonists containing diamino dicarboxylic acid

bridge residues. This type of compound and the scope of the problem to be solved are decisively different from the compounds and the scope of the present invention. Therefore, Applicants respectfully submit that the Lange et al. is not properly a prior art reference. See *In re Rouffet*, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998). As Lange et al. cannot be used to establish a prima facie case of obviousness, the rejection under 35 U.S.C. 103(a) should properly be withdrawn.

Even if Lange et al. is a proper prior art reference in connection with the present invention, according to Alberts et al., the bridging technique with half equivalent 2,7-bis(Boc-amino) suberic acid coupled to one equivalent of lysine (2Cl-Z-protected) attached to the synthesis resin appears slow and takes place over up to 4 days. See Alberts et al. p. 368, first paragraph. Applicants submit the reason for this slow reaction is not known, but for a person skilled in the art of peptide synthesis these facts clearly point away from employing general bridging technique. However, the prejudice that the bridging reaction should be a difficult reaction as such is probably based on a misinterpretation of the necessary conditions for the reaction. Since only half an equivalent can be used in a simple bridging reaction, the rate of reaction decreases as the reaction progresses and will at the end of the reaction be slow because of the very low concentration of the reacting dicarboxylic acid. Thus, it is necessary to couple for about 12 hours to achieve completion of the coupling reaction, which is in contrast to most SPPS (solid phase peptide synthesis), where reactions may be completed within a short time, e.g. 30 minutes, because an excess of reagent can be used.

Applicants submit in contrast to what might be expected from the reports by Lange et al. and by Alberts et al., the Applicants have surprisingly found no problems bridging

peptide chains longer than four amino acid residues. This is demonstrated in the examples with different dicarboxylic acids and with examples of peptide chains with different composition and of different length. Thus, imino diacetic acid (Examples 1, 2 and 6) and 3-amino-glutaric acid (Examples 3, 4 and 5) are used together with a 10-mer peptide, a 17-mer peptide and a 20-mer peptide, glutaric acid and tricarballylic acid with 15-mer peptides including non-natural amino acids (Examples 7 and 8), and 3-amino-glutaric acid with a 10-mer peptide (Examples 9, 10 and 11). In the 2002 article referred to above, the synthesis of further sequences with long chains are exemplified. All examples proceed with high bridging efficiency. These unexpected results differ significantly from that of the prior art.

As the method of the present invention unexpectedly allows the bridging of peptide chains longer than four amino acid residues, the present invention is nonobvious and the rejection under 35 U.S.C. 103(a) should properly be withdrawn.

Request for Interview

Applicants respectfully request either a telephonic or an in-person interview should there be any remaining issues.

Extension of Time

A Petition for an Extension of Time for two (2) months under 37 C.F.R 1.136 and the appropriate fee are submitted herewith to extend the time for responding to the Office Action to March 21, 2003.

Conclusion

Accordingly, in view of the foregoing amendments and remarks, the Examiner is respectfully requested to reconsider and to allow the present claims in order to find this application to be in allowable condition.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By_____
Harvey B. Jacobson, Jr.
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(202) 638-6666
Date: March 21, 2003
Atty. Docket: 162/P63882US0
HBJ/SKS/kpc

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Arne HOLM

Serial No.: New

Filed: Herewith

For: METHOD FOR PREPARING A LIGAND PRESENTING ASSEMBLY (LPA), AN LPA, AND USES THEREOF

PRELIMINARY AMENDMENT TO LESSEN FEES

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Prior to initial examination, please amend the above-identified application as follows:

IN THE CLAIMS

Claim 3, line 1, delete "or 2".
Claim 4, line 1, delete "any one of claims 1-3",
insert --claim 1--.
Claim 5, line 1, delete "any one of claims 1-4",
insert --claim 1--.
Claim 6, line 1, delete "any one of claims 1-5",
insert --claim 1--.
Claim 7, line 1, delete "according to any of claims 2-6",
insert --claim 2--;
line 3, delete "according to claims 1-5".
Claim 9, line 1, delete "any one of claims 1-8",
insert --claim 1--.
Claim 11, line 1, delete "any one of claims 1-10",
insert --claim 1--.
Claim 12, line 1, delete "any one of claims 1-11",
insert --claim 1--.
Claim 14, line 1, delete "any one of claims 1-11",
insert --claim 1--.
Claim 15, line 1, delete "or 13".
Claim 16, line 1, delete "any one of claims 1-11",
insert --claim 1--.
Claim 17, line 1, delete "and 13".
Claim 18, line 1, delete "or 17".
Claim 19, line 1, delete "claims 1-18",
insert --claim 1--.

Claim 21, line 1, delete "or 20";
line 3, delete "of claims 1-20".
Claim 22, line 1, delete "any one of claims 19-21",
insert --claim 19--.
Claim 23, line 1, delete "any one of claims 19-22",
insert --claim 19--.
Claim 25, line 1, delete "any one of claims 19-24",
insert --claim 19--.
Claim 26, line 1, delete "any one of claims 19-24",
insert --claim 19--.
Claim 28, line 1, delete "any one of claims 19-27",
insert --claim 19--.
Claim 29, line 1, delete "any one of claims 19-25",
insert --claim 19--.
Claim 30, line 1, delete "any one of claims 26-28",
insert --claim 26--.
Claim 31, line 1, delete "any one of claims 19-25",
insert --claim 19--.
Claim 32, line 1, delete "any one of claims 26-28",
insert --claim 26--.
Claim 33, line 1, delete "or 32".
Claim 34, line 1, delete "any ones of claims 31-33",
insert --claim 31--.
Claim 35, line 3, delete "any of claim 1-34",
insert --claim 1--.
Claim 36, line 2, delete "as defined in any of claims 1-34".
Claim 37, line 1, delete "or 36".
Claim 39, lines 3-4, delete "any of claims 1-34",
insert --claim 1--.
Claim 40, line 5, delete "any of claims 1-34",
insert --claim 1--.
Claim 41, line 3, delete "any of claims 26-30 or 32-34",
insert --claim 26--.
Claim 42, line 1, delete "any one of claims 19-34",
insert --claim 19--.

Applicant(s): Arne HOLM

REMARKS

The foregoing Preliminary Amendment is requested in order to delete the multiple dependent claims in order to avoid paying the multiple dependent claim fee.

Early action on the merits is respectfully requested.

Respectfully submitted,

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